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Original Article

# Novel mutations of *KCNQ1* in Long QT syndrome

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ABSTRACT

*Background:* Autosomal recessive Long QT syndrome is characterized by prolonged QTc along with congenital bilateral deafness depends on mutations in $K^+$ channel genes. A family of a Long QT syndrome proband from India has been identified with novel *indel* variations.

*Methods:* The molecular study of the proband revealed 4 novel *indel* variations in *KCNQ1*. In-silico analysis revealed the intronic variations has led to a change in the secondary structure of mRNA and splice site variations. The exonic variations leads to frameshift mutations. DNA analysis of the available family members revealed a carrier status.

*Results and Conclusion:* It is thus predicted that the variations may lead to a change in the position of the splicing enhancer/inhibitor in *KCNQ1* leading to the formation of a truncated S2–S3 fragment of KCNQ1 transmembrane protein in cardiac cells as well as epithelial cells of inner ear leading to deafness and aberrant repolarization causing prolonged QTc.



## 1. Introduction

Congenital Long-QT syndrome (cLQTS) is an inherited arrhythmogenic disease characterized on ECG by a prolonged QTc interval. The ECG manifestation reflects an abnormally prolonged ventricular action potential, which can be the substrate for life-threatening arrhythmias that lead to syncope or sudden cardiac death.[1]

Autosomal recessive Jervell and Lange Nielsen syndrome (JLN), characterized by prolonged QTc along with congenital bilateral deafness depends on homozygous or compound heterozygous mutations in either *KCNQ1* and *KCNE1* genes encoding a potassium channel.[2]

The coassembly of these two proteins leads to a slowly activating delayed rectifier potassium channel IKs. *KCNQ1* mapped to chromosome 11p15.5, encodes the larger alpha-

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subunit and *KCNE1* the smaller beta-subunit of the IKs protein. *KCNQ1* consists of 16 exons, spanning 400 kb, has relatively small amino and carboxy termini, and encodes a protein of 676 amino acids. Functional *IK*s channels result from the coassembly of 4 subunits into a tetrameric protein channel that is transported to the myocyte membrane. Each subunit contains 6 membrane-spanning domains (S1 to S6) flanked by amino and carboxyl terminus regions.[3]

To date, numerous mutations have been identified across the coding region of the ion channel genes in JLNS patients but there is a limited data with respect to the Indian population most probably because JLNS, being a recessive disease, is far less prevalent.[4] The precise diagnosis in subclinical patients of LQTS like JLNS warrants molecular analyses in addition to ECG to establish a genotype–phenotype correlation.[5]

In the present context, novel compound heterozygous variations/genetic compounds in a JLN syndrome patient and family members is reported in *KCNQ1* gene with the establishment of genotype–phenotype correlation.

## 2. Materials and methods

### 2.1. Clinical evaluation

The proband, a 6-year-old boy of Indian origin, was referred to the Care Hospitals, Hyderabad with a history of multiple syncopal attacks due to stress since 6 months of age and congenital deafness and dumbness. The proband has a 1 year-old normal sibling and a past history of 2 neonatal and a sudden infant death in older siblings with history of parental consanguinity (Fig. 1).

Laboratory investigations of the proband revealed severe anemia in the proband with a normal blood pressure. The Echo revealed a Patent Foramen Ovale. The electrocardiogram (ECG) showed a prolonged QTc of 520 msec (Fig. 2) and diagnosed with Long QT syndrome following the diagnostic criteria of Schwartz et al whereas the ECG of the parents and

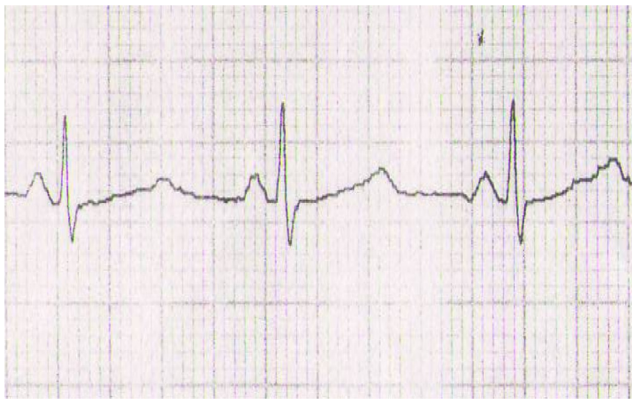


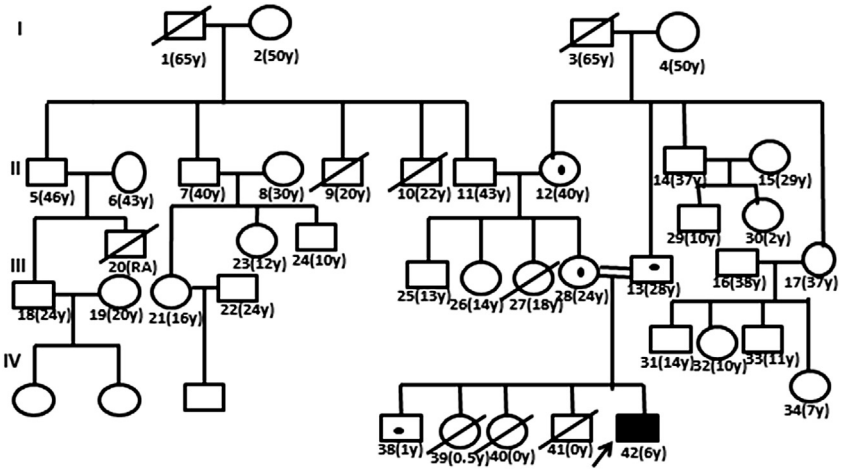
**Fig. 2 – Electrocardiogram of LQTS proband showing a prolonged $QT_C$ of 520 msec.**

the maternal grandparents was found to be normal.[6] (The proband was put on beta-blockers and pacemaker as recommended by the consultant cardiologist.)

Since, JLN syndrome is an autosomal recessive disorder, peripheral blood samples of the proband and the available family members (I-3, II-11, II-12, II-13, III-28, IV-38, IV-42) were collected for DNA analyses after obtaining Institutional Ethics Committee, Dept. of Genetics, Osmania University, India clearance and informed written consent from the proband and his family members. 100 control blood samples without any history of cardiovascular or systemic conditions were collected from Osmania General Hospital, Hyderabad for comparative analysis.

### 2.2. Molecular analyses

Genomic DNA was isolated from peripheral blood samples by following standard protocols in 100 controls proband and his family members. The DNA sequences corresponding to *KCNQ1* gene and *KCNE1* gene were amplified using the primer sets as described by Syrris et al.[7] Fragments were amplified on




**Pedigree of the patient showing consanguinity and neonatal deaths**
**'.' – Sequencing analysis revealed heterozygous genotypes; RA-road accident**

**Fig. 1 – Pedigree of proband.**

Eppendorf Thermal cycler Gradient in the presence of 1 U Taq DNA polymerase, 0.2 mM deoxyribonucleotide, 1.5 mM $MgCl_2$, 100 ng forward and reverse primers and genomic DNA and the PCR products were subsequently screened by Single Stranded Conformational Polymorphism (SSCP) according to standard procedures and the gels were visualized with silver-staining.

### 2.3. *In-silico analysis*

The DNA samples exhibiting a variation in the SSCP pattern were commercially sequenced and the mutations identified were subjected to in-silico analysis to elucidate the effect of the variation on the primary, secondary, 3D and the trans-membrane structure of the protein. In-silico analysis was also carried out to elucidate the mRNA secondary structure changes, splice site changes and the possible binding site variations for SnRNP's involved in spliceosome formation caused by the intronic and exonic variations.

## 3. Results

### 3.1. *Molecular results*

The SSCP patterns variations were observed in the proband, his parents, sibling and his maternal grandmother only in the Exons 3 and 4 of *KCNQ1* gene (Fig. 3A and B). KCNE1 has also been screened simultaneously to identify variations, however, no variations were observed in KCNE1 gene.

On commercial sequencing, the electropherogram of the proband revealed variations in Intron 3, Exon 3 and Exon 4 of

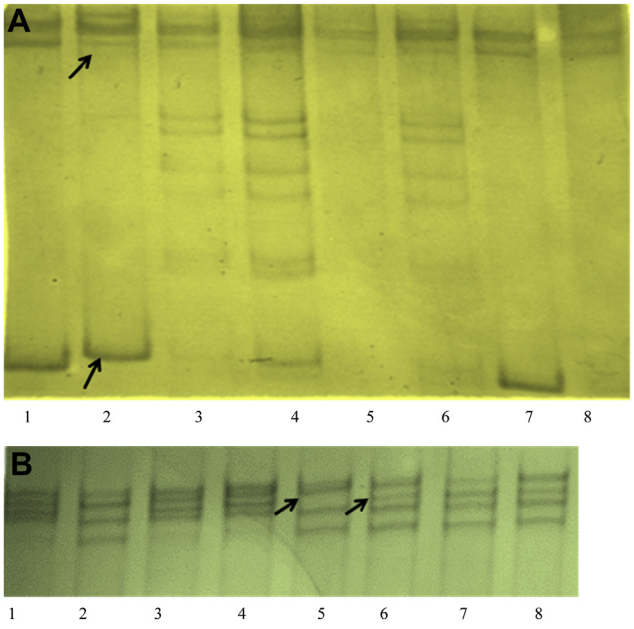



**Fig. 3 – A: SSCP pattern of Exon-3 of *KCNQ1* Lane 1–8 in order (from left): Control, proband, father, mother, sibling, maternal grandmother, maternal grandfather, paternal grandmother. B: SSCP pattern of Exon-4 of *KCNQ1* Lane 1–8 in order (from left): Control, maternal grandmother, maternal grandfather, paternal grandmother, proband, father, mother and sibling.**

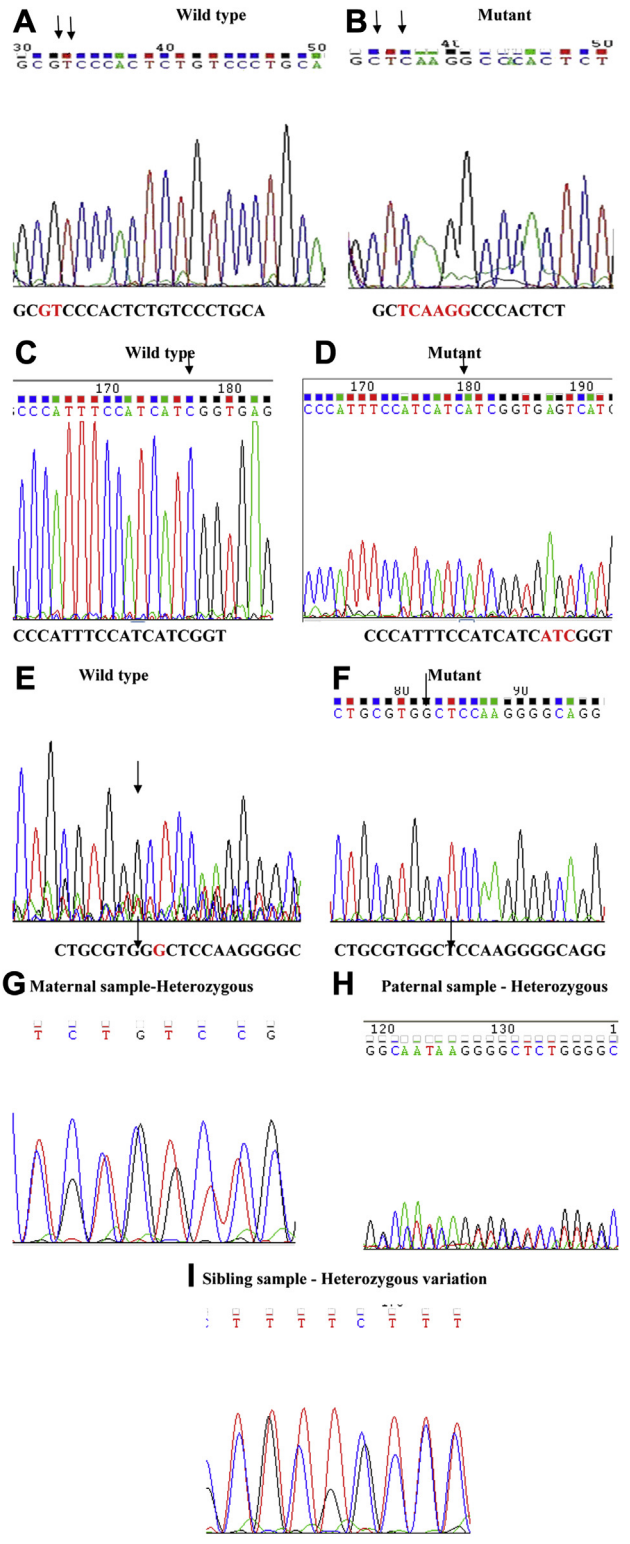



**Fig. 4 – (A–G): Electropherogram of control (A) and mutant (B) revealed the deletion of 'G' at −20 and insertion of 'CAAGG' between −19 and −18 upstream of Exon 3 i.e. in Intron 3. electropherogram of control (C) and mutant (D) revealing an insertion of 'ATC' in Exon 3. electropherogram of control (E) and mutant (F) showing the deletion of 'G' in Exon 4, the chromatogram of maternal heterozygous sample (G), paternal heterozygous sample (H), sibling heterozygous sample (I).**

*KCNQ1* gene for which a reference SNP number (rs number) was registered with **dbSNP**.

The NCBI BLAST revealed the following homozygous variations:

1) Deletion of 'G' **(IVS3-20delG)** [rs181951164] (Fig. 4A and B),
2) An insertion of 'CAAGG' **(IVS3-18_-19insCAAGG)** in Intron 3 [rs187358307] (Fig. 4A and B),
3) An insertion of 'ATC' **(2531968_2531969insATC) in** Exon 3 of *KCNQ1* [rs191143265] (Fig. 4C and D), and
4) A deletion of 'G' **(2532597delG)** in Exon 4 of *KCNQ1* [rs182975255] (Fig. 4E and F).

While the electropherograms of the parents, sibling and maternal grandmother revealed a carrier status of the sequence (Fig. 4G).

### 3.2. *In-silico analysis*

#### 3.2.1. *Splice site prediction*

Splice site analysis was carried out using the online tool www.cbs.dtu.dk/services/NetGene2/ to evaluate the effect of genetic variations wherein predictions revealed a change in the position of the splice site. The donor splice site changed from 100th position to 104th position and the acceptor splice site changed from 15th position to 19th position in the mutant (Table 1).

#### 3.2.2. *Splicing rainbow prediction*

Since, the variation lies close to the donor splice site, it is possible that it could be a part of a possible binding site for SnRNP's involved in spliceosome formation. The sequence was therefore subjected to splicing rainbow software EBI Databases ASD ALTERNATIVE SPLICING (www.ebi.ac.uk/asd-srv/wb.cgi) (Fig. 5).

Splicing rainbow analysis revealed that the variation lies in a putative binding site for hnRNP.I, hnRNP.K, SRp20, SRp40, SRp55, ASF/SF2 and SC35 which clearly highlights the altered regulation (Table 2).

#### 3.2.3. *RNA secondary structure prediction*

Since, the variation lies in the intronic sequence, the RNA secondary structure predicted using GENEBEE software (Table 3) revealed the free energy of the mRNA in the mutant structure (−46.5 kkal/mol) to be lower than that of the wild-type mRNA secondary structure (−35.9 kkal/mol), with the stabilization increasing manifold. The free energies of the mRNA stems of the mutant did not match with the wild-type. The mutation has apparently altered the mRNA secondary structure resulting in a truncated protein.

### 3.3. *Protein structure prediction of Exon 3 variation*

In-silico studies revealed that the insertion of a codon in the Exon 3 of KCNQ1 may lead to the addition of an amino acid, Isoleucine after the 42nd amino acid ( *p.Ilu201_Asp202insIlu*) in the protein primary structure prediction (http://asia.ensembl.org).

#### 3.3.1. *Wild type protein primary structure encoded by 3rd exon*

EIVLVVFFGTEYVVRLWSAGCRSKYVGLWGRLRFARKPISII.

#### 3.3.2. *Mutant protein primary structure encoded by 3rd exon*

EIVLVVFFGTEYVVRLWSAGCRSKYVGLWGRLRFARKPISIII.

#### 3.3.3. *Wild type protein secondary structure encoded by 3rd exon*

The primary protein structures were subjected to the secondary structure prediction tool i.e. The PSIPRED (http://bioinf.cs.ucl.ac.uk/psipred/).

#### 3.3.4. *Mutant protein secondary structure encoded by 3rd exon*

The protein secondary structure prediction revealed an increase in coils due to the addition of an amino acid when compared to the wild type (Fig. 6A and B).

### 3.4. *Protein structure prediction of Exon 4 variation*

#### 3.4.1. *Wild type protein primary structure encoded by 4th exon*

DLIVVVASMVVLCVGSKGQVFATSAI.

#### 3.4.2. *Mutant protein primary structure encoded by 4th exon*

DLIVVVASMVVLCVAPRGRCCHVGHQ.

The protein primary structure prediction shows that the deletion of a nucleotide 'G' **(2532597delG)** leads to a frameshift

**Table 1 – Splice site predictions.**

| Wild | | | | | Mutant | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Donor site predictions | | | | | Donor site predictions | | | | |
| Start | End | Score | Exon | Intron | Start | End | Score | Exon | Intron |
| 100 | 114 | 0.77 | gcagcaa**gt**acgtgg | | 104 | 118 | 0.77 | gcagcaa**gt**acgtgg | |
| 156 | 170 | 0.99 | atcatc**ggt**gagtca | | 163 | 177 | 0.99 | atcatc**ggt**gagtca | |
| Acceptor site predictions: | | | | | Acceptor site predictions: | | | | |
| Start | End | Score | Intron | Exon | Start | End | Score | Intron | Exon |
| 15 | 55 | 0.83 | cgtcccactctgtccctgc**a**<br>**gg**agatcgtgctggtggtgtt | | 19 | 59 | 0.68 | aggcccactctgtccctgc**ag**<br>gagatcgtgctggtggtgtt | |

Acceptor and donor sites-in bold.

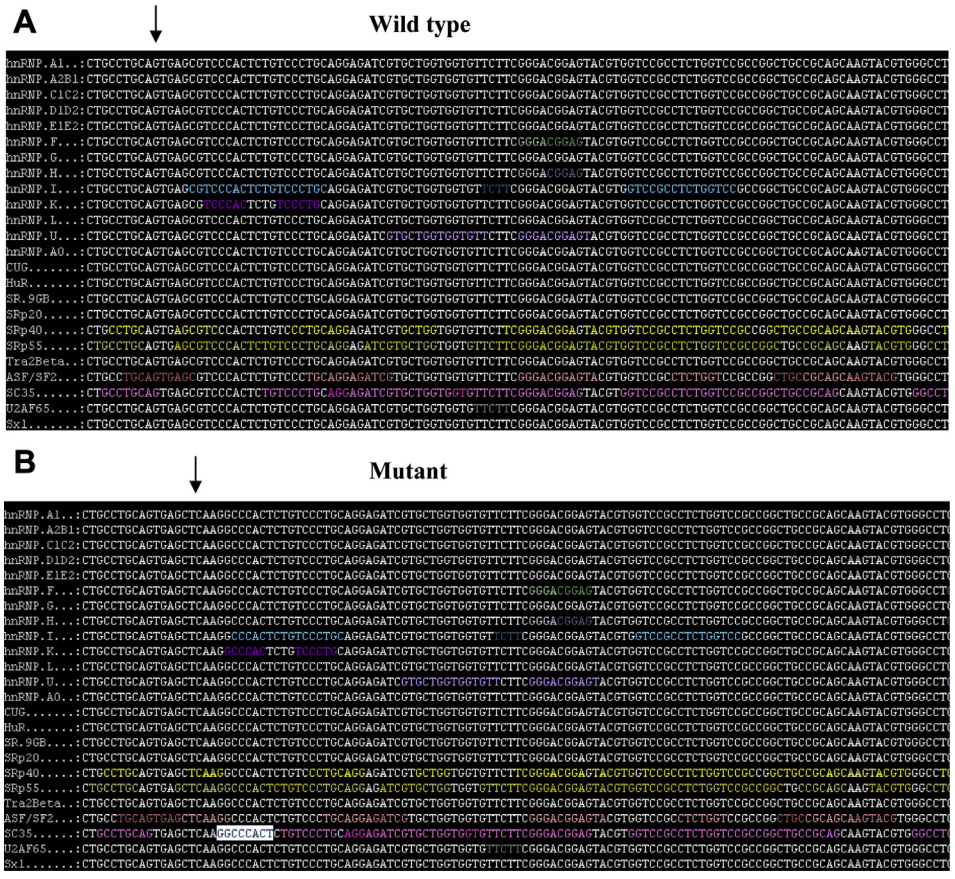


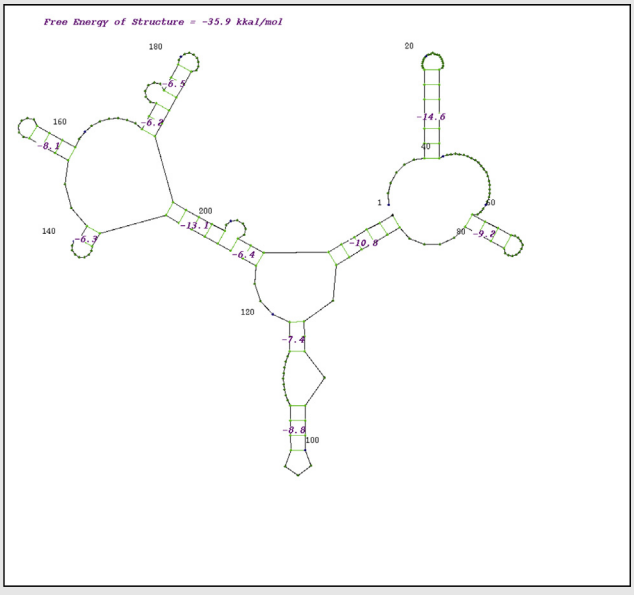

**Fig. 5 – The change in binding sites of various proteins. As seen clearly there is change in binding sites of various proteins (A-wild type and B-mutant) that play a role in regulation (refer Table 2).**

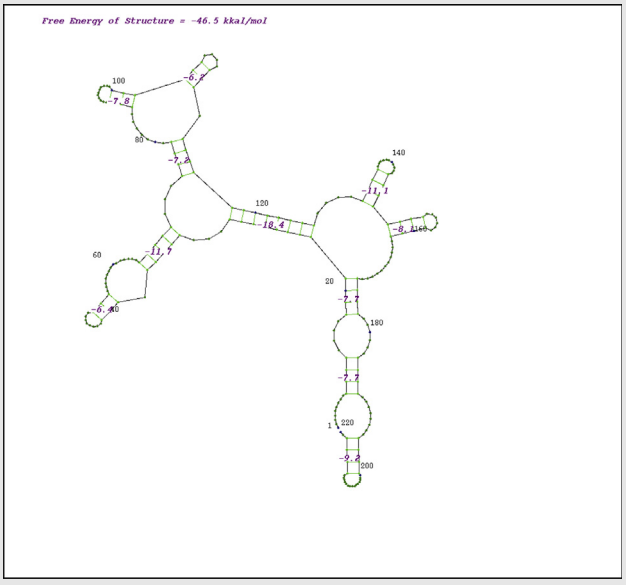
**Table 2 – The variation (indicated in red) in binding sites of various spliceosome complex proteins between wild type and mutant. As seen clearly there is variation and also creation of new binding sites of various proteins that play a role in regulation.**

| Protein | Wild | Mutant |
|---|---|---|
| hnRNP. I | CGTCCCACTCTGTCCCTGC | CCCACTCTGTCCCTGC |
| hnRNP.K | TCCCAC | GCCCAC |
| SRp 20 | TCCATCATCGGTG | TCCATCATCATCGGTG |
| SRp40 | AGCGTC<br>TCCATCATC | TCAAG<br>TCCATCATCATC |
| SRp55 | AGCGTCCCACTCTGTCCCTGCAGG<br>TCCATCATCGG | GCTCAAGGCCCACTCTGTCCCTGCAGG<br>TCCATCATCATCGG |
| ASF/SF2 | - | CTCAAGG |
| SC35 | - | GGCCCACT |

**Table 3 – RNA secondary structure prediction.**

| Control | | | Mutant | | |
|---|---|---|---|---|---|
| Stem- 1 with energy – 14.600000 Kkal/mol | | | Stem- 1 with energy – 18.400000 Kkal/mol | | |
| 7 | 13 | CCTGCAG | 22 | 29 | AGGCCCAC |
| 39 | 33 | GGACGTC | 125 | 118 | TCCGGGTG |
| Stem- 2 with energy – 13.100000 Kkal/mol | | | Stem- 2 with energy – 11.700000 Kkal/mol | | |
| 126 | 130 | GGGCG | 33 | 37 | GTCCC |
| 198 | 194 | CCCGC | 71 | 67 | CAGGG |
| Stem- 3 with energy – 10.800000 Kkal/mol | | | Stem- 3 with energy – 11.100000 Kkal/mol | | |
| 86 | 91 | CTGGTC | 130 | 133 | GGGC |
| 213 | 208 | GACCAG | 148 | 145 | CCCG |
| Stem- 4 with energy – 9.200000 Kkal/mol | | | Stem- 4 with energy – 9.200000 Kkal/mol | | |
| 64 | 67 | GGAC | 196 | 199 | GGTC |
| 81 | 78 | CCTG | 218 | 215 | CCAG |
| Stem- 5 with energy – 8.800000 Kkal/mol | | | Stem- 5 with energy –8.100000 Kkal/mol | | |
| 97 | 100 | GCTG | 149 | 152 | GGAA |
| 107 | 104 | CGAC | 162 | 159 | CCTT |
| Stem- 6 with energy – 8.100000 Kkal/mol | | | Stem- 6 with energy – 7.800000 Kkal/mol | | |
| 145 | 148 | GGAA | 86 | 88 | GCC |
| 158 | 155 | CCTT | 102 | 100 | CGG |
| Stem- 7 with energy -7.400000 Kkal/mol | | | Stem- 7 with energy – 7.700000 Kkal/mol | | |
| 93 | 95 | GCC | 18 | 21 | CTCA |
| 119 | 117 | CGG | 177 | 174 | GAGT |
| Stem- 8 with energy – 6.500000 Kkal/mol | | | Stem- 8 with energy – 7.700000 Kkal/mol | | |
| 176 | 178 | CCT | 10 | 13 | GCAG |
| 190 | 188 | GGA | 187 | 184 | CGTC |
| Stem- 9 with energy – 6.400000 Kkal/mol | | | Stem- 9 with energy – 7.200000 Kkal/mol | | |
| 123 | 125 | TGG | 75 | 78 | GTAC |
| 207 | 205 | ACC | 117 | 114 | CATG |
| Stem- 10 with energy – 6.300000 Kkal/mol | | | Stem- 10 with energy – 6.400000 Kkal/mol | | |
| 131 | 132 | GC | 39 | 41 | GCA |
| 142 | 141 | CG | 52 | 50 | CGT |
| Stem- 11 with energy – 6.200000 Kkal/mol | | | Stem- 11 with energy – 6.200000 Kkal/mol | | |
| 167 | 169 | TGA | 103 | 105 | TGC |
| 193 | 191 | ACT | 112 | 110 | ACG |



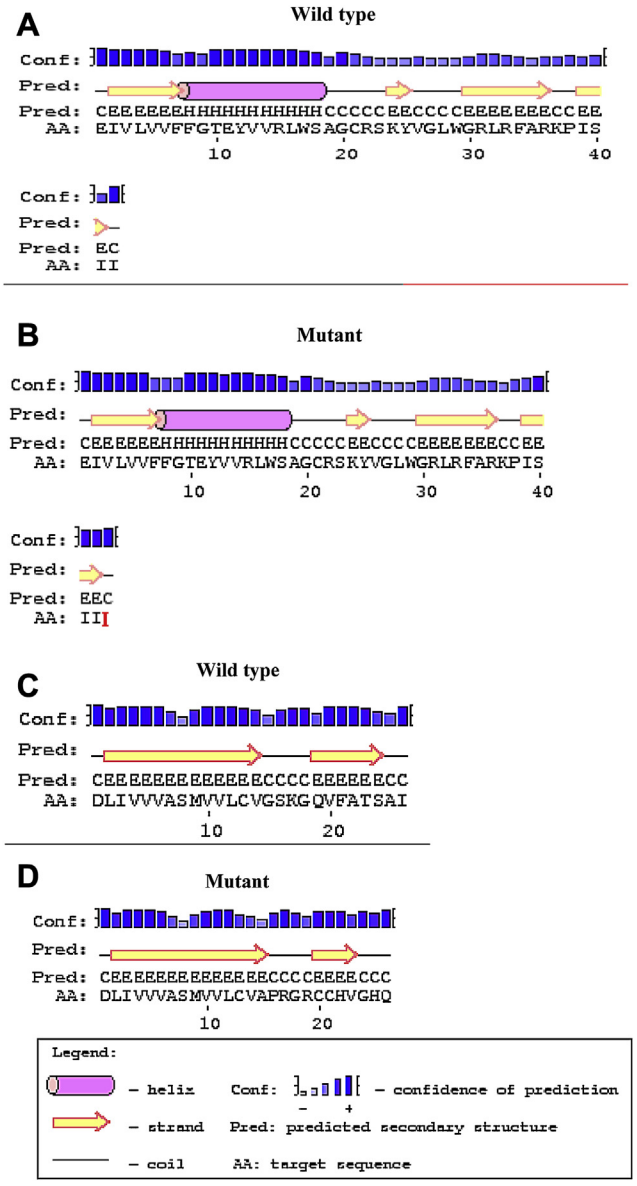



**Fig. 6 – A: Wild type protein secondary structure encoded by 3rd exon. B: Mutant protein secondary structure encoded by 3rd exon. C: Wild type protein secondary structure encoded by 4th exon. D: Mutant protein secondary structure encoded by 4th exon.**

mutation from the site of deletion in the Exon 4 of *KCNQ1* leading to *p.Ala216fs*.

#### 3.4.3. *Wild type protein secondary structure encoded by 4th exon*

The primary protein structures were subjected to the secondary structure prediction tool i.e. The PSIPRED (http://bioinf.cs.ucl.ac.uk/psipred/).

#### 3.4.4. *Mutant protein secondary structure encoded by 4th exon*

The secondary protein structure prediction of Exon 4 indicates a completely altered secondary structure of the protein with an increase in coils and reduction in the strands of the protein when compared to the wild type (Fig. 6C and D).

### 3.5. *3-Dimensional structure prediction of KCNQ1 protein*

The assembly of the complete *KCNQ1* protein when compared to the wild type structure was different with the incorporation of the variant amino acids wherein an increase in number and size of beta sheets was associated with a reduction in size of alpha-helices and replacement of alpha-helices by beta sheets which contributed to an increase in size of loops (Fig. 7A and B).

### 3.6. *Transmembrane structure prediction of KCNQ1*

Since, *KCNQ1* is a transmembrane potassium channel protein and Exon 3 and 4 encode the S2 and S2–S3 transmembrane

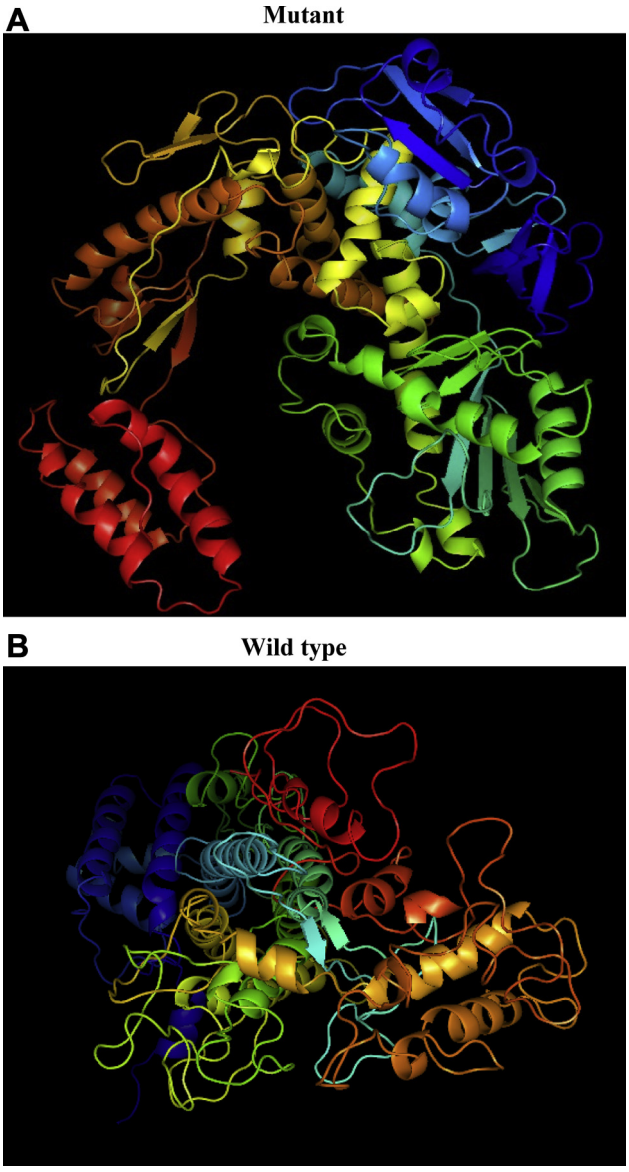



**Fig. 7 – A: 3D structure of mutant protein. B: 3D structure of wild type protein.**

domains of *KCNQ1*, respectively; the effect of frameshift mutations on the transmembrane structure of *KCNQ1* could be predicted (**The PSIPRED** http://bioinf.cs.ucl.ac.uk/psipred/).

The software tool predicted a decrease in number of the transmembrane domains with the S4 transmembrane domain being lost, truncated S2–S3 fragment formation and the N-terminal position shifted from intracellular to extracellular region of *KCNQ1* when compared to the wild type (Fig. 8A and B).

## 4. Discussion

The proband referred as a 6-year-old boy was categorized as a patient of JLN syndrome a recessive form of Long QT syndrome based on the clinical diagnostic criteria with a history of parental consanguinity, neonatal sibling deaths, age at onset of 6 months and deafness associated with mutations in *KCNQ1* gene.[8,9] Mutations associated with JLN syndrome were also reported in Chinese families and other populations.[3,5,10–13]

*KCNQ1* encodes for potassium channel proteins and is primarily localized to the membrane spanning domains and the pore region affecting the heart, inner ear leading to prolonged QTc and deafness.[14,15]

The study reports novel genetic variations in the Intron 3, Exon 3 and Exon 4 of *KCNQ1* in a 6-year-old proband of Indian origin. The patient harboring the homozygous recessive variations has a history of syncope triggered by exercise/emotional stress while the parents, sibling and grandparents of the proband were asymptomatic, but their electropherograms revealed a heterozygosity for the variation. The present study is the first to report on compound heterozyosity/genetic compounds in the proband.

In-silico analysis revealed variations in splice site scores, mRNA secondary structure, hnRNPs and SR proteins binding sites clearly pin-pointing to altered gene regulation associated with protein structure and function variations.

Further, the 3D structure alterations observed by In-silico analysis emphasize an increase in number of beta sheets, loops and decrease in number and length of alpha helices leading to a truncated protein. The aberrant channel may lead to abnormal secretion of potassium in the endolymph of the scala media, which is necessary for normal hearing thus, leading to deafness in the proband.[16–18]

This can be explained on the basis of localization of transmembrane channel with altered shift in N-terminal position and a loss of S4 fragment and truncated S2–S3 fragment. The impact of genetic variations on the protein clearly establishes the potassium channel defects causing JLN syndrome with the impaired efflux of potassium affecting the heart and ear. The study also lays emphasis on the developmental gene implications and the epigenetic modifications of these genes in the

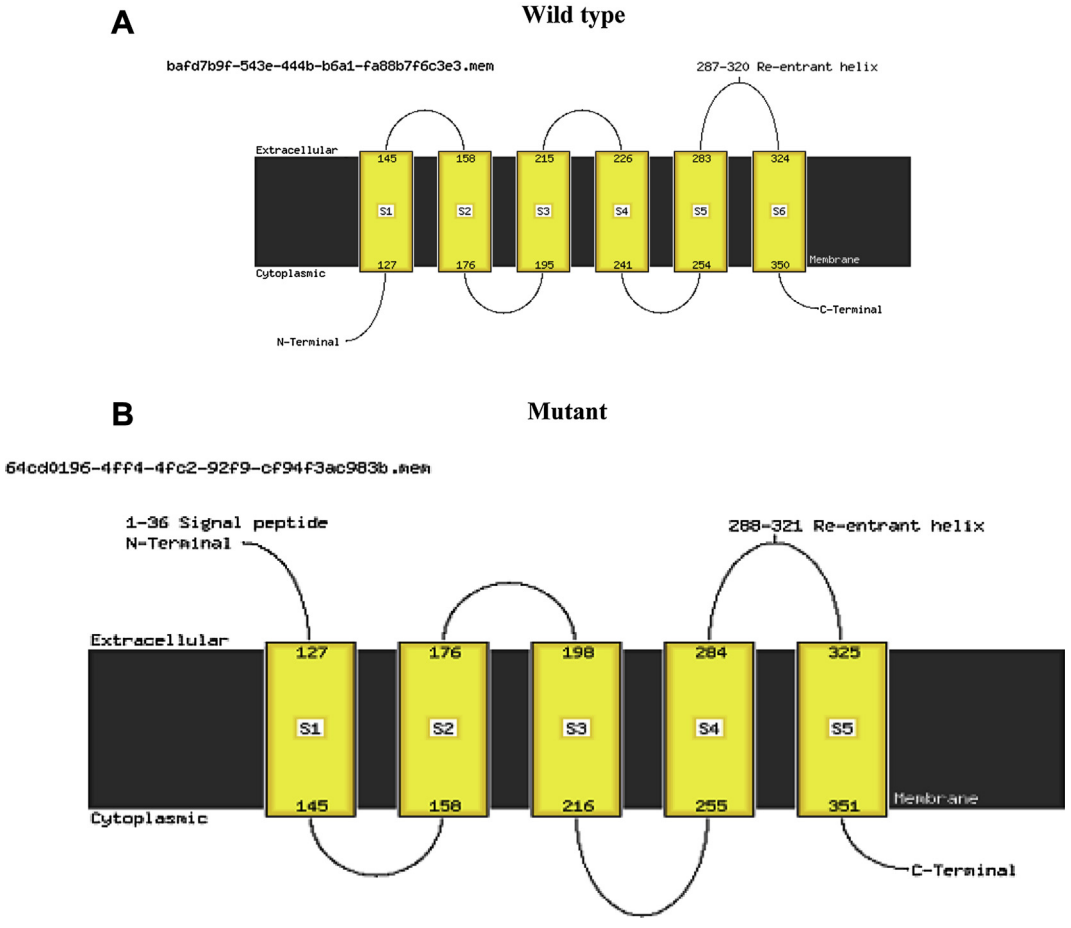



**Fig. 8 – A: Transmembrane structure of wild-type protein. B: transmembrane structure of mutant (Exon 3 + Exon 4 variations) protein.**

onset of JLN syndrome. The pathogenic nature of these variations needs to be elucidated by functional studies.

## 5. Conclusion

We report a Jervell–Lange Neilson syndrome with congenital deafness, prolonged QTc, family history of sudden deaths, consanguinity and compound heterozygosity in *KCNQ1*. The electropherogram of the parents, sibling and maternal grandmother revealed a heterozygous state while the variations in the proband are present in a recessive form. In-silico analysis also revealed the variations may lead to a change in the secondary structure of mRNA and changes the position of splice site. The variations also lead to a change in the position of the splicing enhancer/inhibitor in *KCNQ1* and exonic variations may lead to the formation of a truncated S2–S3 fragment of KCNQ1 transmembrane protein in cardiac cells as well as epithelial cells of inner ear leading to deafness and aberrant repolarization causing prolonged QTc. Functional studies are warranted to elucidate the pathogenic nature of the variations.

## Ethics committee approval

The study has been approved by the Institutional Ethics Committee, Dept. of Genetics, Osmania University, India.

## Author's contributions

**S F Q** has carried out the molecular analysis described in this manuscript and has compiled the manuscript. **A A** has carried out the in-silico analysis described in this manuscript. **A V** has interpreted the results described in this manuscript. **M P J** was involved in the critical revision of the manuscript with respect to the clinical data. The proband described in this manuscript has been diagnosed for LQT syndrome by **C V** as he was presented at his hospital. **K T** has carried out the sequencing analysis of the samples described in this manuscript. As the corresponding author, the concept, design and compilation of this manuscript has been carried out by **P N**.

## Conflicts of interest

All authors have none to declare.

## Acknowledgment

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